REMARKS

Claims 62 and 67-72 have been canceled, and Claims 24 and 63-66 have been amended to point out with more particularity and clarity the subject matter regarded by the Applicant as his invention. In amending Claim 24 and in canceling Claims 67-72 to focus with more particularly and clarity on one aspect of the invention as originally filed, Applicant respectfully reserves the right to file subsequent applications(s) to protect the invention commensurate with the scope as originally filed

In the preamble of claim 24, the subject genus of diseases or disease susceptibility traits has been amended for greater particularity and clarity to be defined as those diseases "in which at least about 10% of affected individuals have a germline mutation in one of two or more subject genes, wherein said germline mutation is selected from the group consisting of truncation-causing mutations and mutations that cause allelic loss." Support for that amendment can be found in the Specification at least at page 5, line 18 to page 8, line 1, particularly at page 6, line 3 to page 7 line 5; and at page 18, line 30 to page 24, line 26, particularly at page 18, line 30 to page 19, line 24. Within those passages, a representative immunoassay of this invention to detect susceptibility to hereditary non-polyposis colon cancer (HNPCC) in humans is described:

> This invention addresses one of the problems of inadequate management of CRC by providing improved and earlier diagnosis of the most common form of hereditary colon cancer, **HNPCC, a disorder which accounts for about 10% of patients that have been diagnosed with CRC**.

[Specification, page 7, lines 2-5; emphasis added.]

> Because there is at least 90% penetrance associated with **germline MMR mutations (i.e. HNPCC patients)**, almost all carriers will develop cancer during their lifetimes.

[Specification, page 19, lines 1-3; emphasis added.]

> Another recommended target population for the immunoassay methods of this invention are patients identified as having CRC (**10% of CRC patients are predicted to carry MMR mutations**).

[Specification, page 6, lines 21-23; emphasis added.]

> In the case of screening for the HNPCC susceptibility trait, the amounts of MLH1 and MSH2 wild-type proteins (the expression products of the two major MMR genes) are measured from a sample from an individual, e.g. from freshly prepared lymphocytes. **Almost all individuals with a germline MMR mutation will have 100% of one of those two full-length MMR proteins but only 50% of the other full-length protein**.

[Specification, page 6, lines 4-9; emphasis added.]

> **Many of the known mutations in MMR proteins result in truncated proteins**.

[Specification, page 23, lines 3-4; emphasis added.]

> **About 10% of all CRC cases are estimated to be hereditary cancers**. . . . **Most hereditary colon cancer is associated with germline MMR mutations**.

[Specification, page 19, lines 15-17; emphasis added.]

As indicated by the above passages from the Specification, the exemplary subject disease colorectal cancer is one in which at least about 10% of patients have a germline mutation in mismatch repair genes, many of which mutations are found to result in truncated proteins. If the subject disease is hereditary colorectal cancer, nearly all of the patients are predicted to have a germline mutation in one of the mismatch repair genes.

More general support for the above amendment to the preamble of Claim 24 can be found at page 31, line 6 to page 37, line 2, wherein the percentage of patient cases having "truncation-causing mutations and mutations that cause allelic loss" are given for the "other hereditary and genetic disorders (cancer and non-cancer)" listed at pages 7-8 of the specification, that may be screened according to the immunoassays of the invention [Specification, page 7, lines 6-9]. The reported percentage of cases with such mutations (i.e., truncations and allelic loss) vary from **15%** [cystic fibrosis cases with CFTR truncations; page 32, lines 20-26] **to 95%** [Duchenne muscular dystrophy cases with DMD truncations; page 32, line 28 to page 33, line 8; and polycystic kidney

disease cases with PKD1 truncations; page 34, lines 15-22]. For the diseases mentioned in the instant specification, all of the reported percentages of cases having truncation mutations or allelic loss fall within the limitation of Claim 24 of "at least about 10% of affected individuals."

Support for the phrase "wherein said germline mutation is selected from the group consisting of truncation-causing mutations and mutations that cause allelic loss" of amended Claim 24 can be found throughout the Specification, particularly at page 7, lines 6-9, which read: "The immunoassays of this invention may be adapted to measure full-length (wild-type) proteins associated with many other hereditary and genetic disorders (cancer and non-cancer) that are due to mutations that cause protein truncation (germline and aquired) or cause the absence of allelic protein expression."

The preamble of independent claim 24 has also been amended for particularity and clarity to replace the limitation "wherein each of said subject genes has been associated with such a disease or such a disease susceptibility trait" with the limitation "wherein each of said subject genes is known to have said germline mutation in individuals affected with said disease or said disease susceptibility trait . . .", to indicate that the two or more subject genes are associated with the same disease or the same disease susceptibility trait (the subject matter of canceled Claim 62). Support for that amendment can be found in the instant application at least at page 8, lines 8-22, particularly at lines 14-22, which state:

> The reference protein can be . . . the expression product of another subject gene that could also be associated with the disease or disease susceptibility to which the assay is directed. In that latter embodiment, the assay could be characterized as a form of differential diagnosis/prognosis, determining in one assay which of several genes is affected by a disease-associated mutation.

[Emphasis added.]

Claims 63-66, previously depending from now canceled Claim 62, have been amended to depend from independent Claim 24 as discussed above.

Applicant respectfully submits that no new matter has been entered by the cancellation of Claims 62 and 67-72 and the amendments to Claims 24 and 63-66.

Withdrawal of 103(a) Rejection in Section 3 of Final Office Action

Applicant respectfully acknowledges, appreciates and agrees with the Examiner's withdrawal of the 35 USC 103(a) rejection, based on Glendening et al. in view of Nozawa.

35 USC 112, 1st Paragraph Rejection

The Final Office Action maintains the rejection of Claims 24-28, 32-35, 37-44, 55-57 and 59-72 "under 35 USC 112, first paragraph, as failing to comply with the written description requirement. . . ." Further, the claims are rejected for containing new matter as "[t]he claims, as currently amended are not fully described by the specification. . . ." [Final Office Action, Section 4, page 3.] Applicant respectfully traverses, pointing out that independent Claim 24 has been amended to delete the phrase "has been associated with," to which phrase the Examiner objects, to point out with more particularity and clarity the subject matter regarded by the Applicant as his invention. Applicant respectfully points out that the subject genus of diseases and disease susceptibility traits has been clarified by the amendments to Claim 24, which amendments are supported in the Specification.

The Office Action states on page 3, that

> the amendment introduces new matter because the phrase "has been associated" is different in scope from the concept presented in the specification of a theoretical association between a heterozygous mutation that may produce an about 50% decrease in a level of a protein.

[Office Action, Section 4, page 3.] For increased clarity and particularity, Applicant has amended the preamble of independent Claim 24 to indicate that the claimed invention is directed to a method for detecting a disease or disease susceptibility trait, wherein the subject genus of diseases and disease susceptibility traits is defined by the percentage of cases found to have mutations in specific genes that result in protein truncations or allelic loss:

> A method of detecting a disease or a disease susceptibility trait in an organism, wherein said disease or said disease susceptibility trait is one in which at least about 10% of

> affected individuals have a germline mutation in one of two or more subject genes, wherein said germline mutation is selected from the group consisting of truncation-causing mutations and mutations that cause allelic loss, and wherein each of said subject genes is known to have said germline mutation in individuals affected with said disease or said disease susceptibility trait. . . .

Applicant respectfully submits that the definition of the subject genus of diseases and disease susceptibility traits in Claim 24 is clear and supported by the specification.

Applicant respectfully points out that the patent case law is clear that the written description for a genus is sufficient if ones of skill in the art to which the invention pertains can "visualize or recognize the identity of the members of a genus." [Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398 at 1406 (Fed. Cir. 1997); see also, Amgen Inc. v. Hoechst Marion Roussel Inc., 6 USPQ2d 1385 (Fed. Cir. Jan. 6, 2003).] Applicant respectfully submits that ones of skill in the art can "visualize or recognize the identity of the members of . . . [the] genus" of diseases and disease susceptibility traits to which the amended Claims 24 and its dependent claims apply.

Applicant further respectfully points out that the patent case law is clear that an applicant is not required to describe in a specification every conceivable and possible future embodiment of his or her invention. [See, Rexnord Corp. v. Laitram Corp., 60 USPQ2d 1851, 1856 (Fed. Cir. 2001); Amgen Inc. v. Hoeschst Marin Roussel Inc., supra; Sunrace Roots Enter. Co., Ltd. v. SRAM Corp., 336 F.3d 1298 (Fed. Cir. July 17, 2003); and Superguide Corp. v. DirecTV Enterprises, Inc., 69 USPQ2d 1865 (Fed. Cir. Feb. 12, 2004).] A specification may within the meaning of 35 U.S.C. § 112, contain a written description of a genus without describing all species that a claim encompasses, as long as one of skill in the art can "visualize or recognize the identity of the members of . . . [the] genus." [Case law as cited above, id.; see also Cordis Corp. v. Medtronic AVE, Inc., 339 F.3d 1352 (Fed. Cir. August 12, 2003).]

Applicant further respectfully points out that the Applicant has provided experimental evidence supporting the theoretical correlation between the APC gene mutation and its corresponding protein product levels. [Instant specification, page 45, lines 22-29; page 49, line 27 to page 50, line 11.] Pece et al. reported that allelic loss mutations of the endoglin gene resulted in an apparent 50% reduction in endoglin

levels. As mentioned in the previous response by the Applicant (submitted to the PTO on November 15, 2004), in most cases gene product levels correspond to gene dosage: "[I]n general, the amount of transcript produced by a gene is directly proportional to the number of copies of that gene in a cell. That is, for a given gene, the rate of transcription is directly related to the number of DNA templates." [Griffiths et al., An Introduction to Genetic Analysis, Seventh Ed. W. H. Freeman, New York, (2000).[1]] One of skill in the art would expect that mutations "selected from the group consisting of truncation-causing mutations and mutations that cause allelic loss" would result in a 50% reduction in gene expression.

Applicant respectfully concludes that Claim 24 as amended and its dependent claims clearly comply with the written description requirement of 35 USC 112, first paragraph. Applicant respectfully requests that the Examiner reconsider the subject 112, first paragraph rejection in view of the amendments to the claims and the above remarks, and withdraw the subject rejection.

35 USC 103(a) Rejection of Claims 24-28, 32-35, 43, 44, 55-57 and 61

Claims 24-28, 32-35, 43, 44, 55-57 and 61 stand "rejected under 35 USC 103(a) as being unpatentable over Pece [Pece, N. et al. J. Clin. Invest. 100(10): 2568-2579 (November 1997); cited in IDS] in view of Nozawa (U.S. Patent 5,328,826; issued July 12, 1994; filed March 23, 1992)." [Final Office Action, Section 5, page 4.] Applicant respectfully traverses that rejection by first relying on the arguments made in the earlier Amendment dated November 15, 2004 concerning the subject invention. The arguments and remarks made therein, as well as the case law supporting those arguments and remarks, are herein incorporated by reference.

Applicant has amended the preamble of Claim 24 to incorporate the limitation of Claim 62 (now canceled), to claim a method for detecting a disease or disease susceptibility trait associated with a germline mutation in one of two or more

1. www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=iga, Chapter 18, "Mechanisms of Gene Imbalance".

subject genes, wherein the two or more subject genes are associated with the same disease or the same disease susceptibility trait:

> A method of detecting a disease or a disease susceptibility trait in an organism, wherein said disease or disease susceptibility trait is one in which at least about 10% of affected individuals have a germline mutation in one of two or more subject genes . . . and wherein each of said subject genes is known to have said germline mutation in individuals affected with said disease or said disease susceptibility trait . . .

[Preamble of Claim 24; emphasis added.] As indicated above, Applicant by amending Claim 24 and cancelling Claims 67-72 for more particularity and clarity, thereby focusing on one aspect of the invention as originally filed, respectfully reserves the right to file subsequence application(s) to protect the invention commensurate with the scope as originally filed.

Applicant respectfully submits that the ratios cited in Pece are not the same ratios as those of amended Claim 24, as the reference proteins $\alpha 5\beta 1$ integrin and CD31 are not associated with the germline disease hereditary hemorrhagic telangiectasia type 1 (HHT1), which is associated with the subject gene endoglin. Further, Pece does not refer to the reduction of the expression of any second or more genes as a possible cause of HHT1, nor does Pece suggest determining a ratio of endoglin to ALK-1 in families with any type of hereditary hemorrhagic telangiectasia. Applicant respectfully but forcefully maintains that Pece either alone or in view of Nozawa, certainly does not anticipate independent Claim 24 and the remaining claims which are all dependent on Claim 24, either directly or indirectly. *A fortiori*, Pece, alone or in view of Nozawa, most certainly does not anticipate or render obvious Claim 24, as amended, or its dependent claims.

At page 4 of the Final Office Action, the Examiner states:

> The claimed inventions include within their scope methods where one of the two subject genes is a housekeeping gene, and therefore, read on methods where one of the protein detected is detected for the purpose of ensuring that differences observed in protein levels between different samples is due to an actual difference in protein levels per

> cell and not due to an experimental artifact such as different loading between samples.

[Final Office Action, Section 5, page 4.] Further, the Examiner states that "Nozawa is cited for the purpose of demonstrating that methods for quantitating protein are known in the art and the use of a ratio of a level of a protein of interest to a level of a housekeeping protein is known." [Final Office Action, Section 5, page 4.] Applicant respectfully submits without conceding to the characterization of Nozawa in the office action, that within the context of the invention as presently claimed, a subject gene product detected for use in the ratios of the instantly claimed invention cannot be defined as a housekeeping gene product, as qualified by the office action with regard to Pece et al. and Nozawa. In Pece et al. and Nozawa, a reference protein is detected because it is expected to be unchanged [Pece et al., page 2573, 1st col.], a "substance present in human cells in a substantially constant amount." [Nozawa Abstract.] In the claims as amended, each and every subject gene product is detected because it is suspected of being reduced in level.

Applicant respectfully concludes that neither Pece alone nor in view of Nozawa anticipates or renders the instantly claimed invention obvious, but instead as explained above is evidence of the nonobviousness of the instant invention. Applicant respectfully requests that the Examiner reconsider the subject 103(a) rejection in view of the amendments to the claims and the above remarks, and withdraw this rejection.

CONCLUSION

Applicant respectfully concludes that the claims as amended are in condition for allowance, and earnestly requests that the claims be promptly allowed. If for any reason the Examiner feels that a telephone conference could be helpful, the

Examiner is invited to telephone the undersigned Attorney for Applicant at (415) 981-2034.

Respectfully submitted,

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